UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,149	10/19/2001	R. Preston Mason	2189 P01 US CIP	2552

26486 7590 01/29/2004

PERKINS, SMITH & COHEN LLP
ONE BEACON STREET
30TH FLOOR
BOSTON, MA 02108

EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,149	MASON, R. PRESTON	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 22-65* is/are pending in the application.

4a) Of the above claim(s) *29-56 and 60-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 22-28, 57-59 and 63-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on October 30, 2003 wherein claims 15-21 are cancelled, and claims 1, 4, 6-14, 22-23, 27-28, and 57 have been amended, and claims 63-65 are newly submitted.

Currently, claims 1-14 and 22-65 are pending in this application.

Election/Restrictions

Applicant's affirmation of the telephonic election with traverse of the invention of Group I, claims 1-28 and 57-59, submitted October 30, 2003 is acknowledged.

It is noted that claims 29-56 and 60-62 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, of record in the previous Office Action dated March 20, 2002.

As noted in MPEP § 804.01 (see below).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112.

Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 1-14, 22-28, 57-59 as amended now, and new claims 63-65 are examined on the merits herein.

Applicant's amendment filed on October 30, 2003 with respect to the objection of claims 4-21 and 25-28 made under 37 CFR 1.75 (c) for improper dependent for failing to further limit claim and the employment of parenthetic expression of record stated in the Office Action dated March 20, 2002 have been fully considered and are found persuasive since these claims have been amended to overcome this objection. Therefore, this objection is withdrawn.

Applicant's amendment filed on October 30, 2003 with respect to the rejection of claims 1-28 and 57-59 made under 35 U.S.C. 112 second paragraph for the use of the indefinite expression, i.e., "formulation agents" in the claims of record stated in the Office Action dated March 20, 2002 have been fully considered and found persuasive to remove the rejection since indefinite

expression has been deleted from the claims. Therefore, the said rejection is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14, 22-28, 57-59 as amended now and new claims 63-65, are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (4,879,303) and Bjorge et al. (5,385,929) in view of Jekema et al. (Arteriosclerosis, Thrombosis, and Vascular Biology, Vol. 16, No.3, 1996, p425-430), and Merck Index, for the same reasons of record stated in the Office Action dated March 20, 2002.

Davison et al. (USPN 4,879,303) teaches a pharmaceutical composition comprising amlodipine besylate useful in treating ischemic heart disease, angina or hypertension, see claim 1 and abstract in particular.

Bjorge et al. (USPN 5,385,929) teaches a pharmaceutical composition comprising ortho, meta, para hydoxylated metabolites of atorvastatin and a pharmaceutical carrier useful in inhibiting cholesterol synthesis, treating hypercholesterolemia, atherosclerosis, see claims 12, 18 and abstract.

Davison et al. (USPN 4,879,303) and Bjorge et al. (USPN 5,385,929) taken together do not expressly disclose a phannaceutical composition comprising amlodipine besylate and a hydroxylated metabolite of atorvastatin.

Jekema et al. discloses the evidence for a synergistic effect of calcium channel blockers (CCB) with lipid-lowering therapy in retarding progression coronary atherosclerosis in symptomatic patients with normal to moderately raised cholesterol levels (see particularly the Title of the article and abstract, and the 1st paragraph of the left column at page 426). The lipid-lowering agents employed therein in the combined therapy are HMG-CoA reductase inhibitors such as pravastatin (see the right column of the abstract at page 425 and the 1st paragraph of the right column at page 425 and the 3rd paragraph of the right column at page 426). One of calcium channel blockers employed therein is amlodipine (5 to 10 mg) (see the 3rd paragraph of the right column at page 426). Atherosclerosis is known to have symptoms such as hyperlipidemia according to Jekema et al.

The Merck Index Therapeutic Category and Biological Activity Index lists atorvastatin as a HMG-COA Reductase Inhibitor, belonging to the same therapeutic group as Pravastatin, see THER-10. Further, The Merck Index Therapeutic Category and Biological Activity Index lists amlodipine as well as other calcium channel blockers as antihypertensive agents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ amlodipine besylate with atorvastatin metabolites in a phannaceutical composition.

One of ordinary skill in the art would have been motivated to employ amlodipine besylate with atorvastatin metabolites in a pharmaceutical composition useful in a method of treating cardiovascular diseases such as hypertension, hyperlipidemia and atherosclerosis because atorvastatin is a known HMG Co-A reductase inhibitor and is therefore expected to have therapeutic effects similar to pravastatin. Similarly, amlodipine is a known calcium channel blocker. One of ordinary skill in the art would have been motivated to employ the known antihyperlipidemic metabolites of HMG CoA Reductase inhibitor atorvastatin for exnmple, with the known calcium chnnnel blocker, nmolodipine besylate in a single pharmaceutical composition useful in treating heart disease since the combinations of agents known to be useful individually for the same purpose into a single combination useful for the very same purpose is *prima facie* obvious. In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069 (CCPA, 1980). All actives recited in the claims are known to be useful in the treatment of heart disease.

Therefore, combining all of these active agents in a composition or method useful in treating osteoporosis is prima facie obvious. Moreover, the skilled artisan would combine the two agents because the addition of calcium channel blockers to HMG COA reductase inhibitory therapy is known to have a synergistic effect in treating atherosclerosis.

Response to Argument

Applicant's remarks filed on October 30, 2003 with respect to the rejections made under 35 U.S.C. 103(a) of record stated in the previous Office Action dated March 20, 2002 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant's assertions that there is no teaching or suggestion in the art that these two particular drugs combined in a single pharmaceutical composition for the inhibition of lipid peroxdation in human low density lipoprotein, and that Jukema et al. is a retrospective metanalysis of a clinical investigation and did not provide any experimental data in support of their hypothesis, and at best, be an "obvious to try" specculation have been considered but are not found persuasive.

First, it is noted that such experimental data is not required as a basis of a rejection under 35 U.S.C. 103 for obviousness. Absolute predictability is not required. See *In re Lamberti and Konort*, 192 USPQ 278.

Second, in contrast to applicant's assertions of the rejection is based upon an "obvious-to-try" standard; it is by now well understood that the ultimate conclusion of law that claimed subject matter as a whole would have been obvious under 35 USC 103 may at times properly be drawn from an inference of fact arising from prior art teachings which could be considered an inference that it would be "obvious to try" that which is claimed. In re O'Farrell, 853 F.2d 894, 7 USPQ 2d 1973 (Fed. Cir. 1988); Contour Saws Inc. v. Starrett Co., 444 F. 2d

433, 170 USPQ 433 (Ct.App. 1977); In re Marzocchi, 439 F. 2d 220, 169 USPQ 367 (CCPA 1977); In re Lindell, 385 F. 2d 435, 155 USPQ 521 (CCPA 1967).

In the instant case, as discussed in the previous Office Action and above, Jekema et al. discloses the evidence for a synergistic effect of calcium channel blockers (CCB) with lipid-lowering therapy in retarding progression coronary atherosclerosis in symptomatic patients with normal to moderately raised cholesterol levels (see particularly the Title of the article and abstract, and the 1st paragraph of the left column at page 426). The lipid-lowering agents employed therein in the combined therapy are HMG-CoA reductase inhibitors such as pravastatin (see the right column of the abstract at page 425 and the 1st paragraph of the right column at page 425 and the 3rd paragraph of the right column at page 426). One of calcium channel blockers employed therein is amlodipine (5 to 10 mg) (see the 3rd paragraph of the right column at page 426). Atherosclerosis is known to have symptoms such as hyperlipidemia according to Jekema et al.

Jukema et al. is not merely a hypothesis, but shows the experimental data or testing results of the combination pravastatin and amlodipine to be administered to patients (see page 426 the right column). Thus, Jukema et al. do provide experimental data even though it is not required as a basis of a rejection under 35 U.S.C. 103 for obviousness.

Hence, Applicant's arguments regarding to Jukema's testing results and that Jukema did not provide the motivation to combine the two instant drugs (see page 12-13 of Applicant's remarks), are not convincing. As noted in MPEP 2123,

stating: "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Moreover, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994)

Moreover, atorvastatin is known HMG Co-A reductase inhibitor and known to reduce LDL and VLDL triglycerides and is therefore expected to have therapeutic effects similar to pravastatin.

It must be recognized that any judgment on obviousness takes into account knowledge which was available and within the level of ordinary skill at the time the claimed invention was made.

Thus, the teachings of Jekema et al. have clearly provided the motivation to combine amlodipine and atorvastin in a pharmaceutical composition for

treating atherosclerosis since it is known that a calcium channel blocker in combination with a HMG-CoA reductase inhibitor (a lipid-lowering agent) produces a synergistic effect in retarding progression coronary atherosclerosis according to Jekema et al. Calcium channel blockers such as amlodipine is known to be employed in the combination therapy of Jekema et al. Therefore, one of ordinary skill in the art would have reasonably expected that combining amlodipine and the particular HMG-CoA reductase inhibitor, atorvastin, in a pharmaceutical composition would produce additive therapeutic effects in treating atherosclerosis in a patient, with reasonable expectation of success, based on the clear teaching of Jekema et al.

Further, it has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form a third composition that is to be used for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art. *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. In the instant case, as discussed in the set forth 103(a) rejection above, Therefore, one of ordinary skill in the art would have reasonably expected that combining amlodipine and atorvastin or combining the atorvatatin composition of Bjorge et al. (4,879,303) and the amlodipine composition of Davidson et al. into a single pharmaceutical composition, known useful for the same purpose, i.e., atherosclerosis or ischemic heart disease, in a single composition to be administered would improve the therapeutic effect for treating

atherosclerosis or ischemic heart disease in a patient, absent evidence to the contrary.

The record contains no clear and convincing factual evidence of nonobviousness or unexpected results, i.e., testing data, for the combination method herein over the prior art. In this regard, it is noted that the specification provides no side-by-side comparison with the closest prior art, i.e., comparing with Jekema et al., in support of nonobviousness for the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
January 23, 2004

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

1/26/04